Practice w/ EBM Skills – Skeel

Objectives:

* Review factors that inform ***clinical decision making*** and skills required for EBM
* Review parts of a ***well-built clinical question***
* Practice use of key issues that help determine the ***validity***, ***effect size, and generalizability*** of results of a study
* Analyze strategies when ***real-world experiences*** appear to conflict with EBM

CDM is based on a mix of:

* scientific data: basic and clinical
* experience
* training
* other:
  + reimbursement
  + allure of new technology
  + current opinion
  + bias: failure of payment disclosure
  + marketing – HPV vaccine

Skills required for EBM:

* understand basic statistical methods
* knowing sources of valid info
* efficient literature searching
* application of formal rules of evidence in evaluating clinical literature:
  + critical thinking
  + critical appraisal
* ability to relate evidence from literature to individual patient

6 step EBM process:

1. **The patient** - Start with the patient - a clinical problem or question arises out of care of the patient
2. **The question** - Construct a well built clinical question derived from the case.
3. **The resource** - Select the appropriate resources and conduct a search
4. **The evaluation** - Appraise that evidence for its validity (closeness to the truth) and applicability (usefulness in clinical practice)
5. **The patient** - Return to the patient. Integrate that evidence with clinical expertise, patient preferences and apply it to practice
6. **Self-evaluation** - Evaluate your performance with the patient.

Practice case 1:

1. The patient

-17 year old at 24 weeks gestation during second pregnancy.

-First pregnancy ended in spontaneous abortion.

-Lives with aunt

-Smoked 1 ppd for 2 years; uses occasional marijuana; drinks beer on weekend.

-Wants to quit smoking, since smoker friend delivered a premature baby with complications.

-She asks if nicotine gum will help her quit.

2) Clinical Question:

- would you recommend use of nicotine gum to reduce risk of delivering a low birth weight baby in a 17 year old?

- clinical concerns:

* Smoking doubles risk of delivering low birth weight/premature neonate and incr risk of numerous adverse perinatal and neonatal outcomes
* Behavior intervention yield quit rates <18%

3) the resource: be prepared to discuss characteristics such as:

* Study objective
* Study rationale
* Appropriateness of study design
* Sample inclusion and exclusion criteria
* Randomization and blinding, if any
* Results and interpretation:
  + Statistical validity, clinical importance; such as effect size
* Identification and import of confounding variables
* Study strength and weaknesses

For this case:

- Study objective:

a prospective, randomized, double blind, placebo-controlled clinical trial of the **safety and efficacy** of 2-mg nicotine gum in pregnant smokers.

Chose nicotine formulation because previous work suggested that 2-mg nicotine gum reduced nicotine exposure and generally had a lesser effect on maternal and fetal hemodynamics than ad libitum smoking and may deliver a lower dose of nicotine than a patch.

The **primary outcome** for this study was biochemically confirmed 7-day point prevalence **abstinence rates** at two time points: **after 6 weeks of gum use and at the end of pregnancy.**

Other major endpoints included the birth weight of the offspring and measures of smoking reduction.

Effect size: how much of a diff there was

- Study rationale:

Chose nicotine formulation because previous work suggested that 2-mg nicotine gum reduced nicotine exposure and generally had a lesser effect on maternal and fetal hemodynamics than ad libitum smoking and may deliver a lower dose of nicotine than a patch.

- Study design:

* 194 Pregnant women who smoked daily received behavioral counseling and a random assignment to nicotine gum or placebo, which they were instructed to substitute gum for cigarettes during a 6 week treatment followed by a 6 week taper.
* Measures of tobacco exposure obtained.

- Inclusion and Exclusion criteria

* Inclusion: Age >16, smoking > 1 Cig/day, <26 weeks gestation, stable residence.
* Exclusion: Current illicit drug or alcohol use disorder within preceding month; psychiatrically or medically unstable; twins or other multiple gestation
* Prior approval by the UCONN Institutional Review Board and each of enrollment sites. Why? IRB approval bc it’s a study with human subjects; need them to know about it and get their permission

Balancing variables:

* Maternal age
* Gestational age at entry
* Number of cigarettes daily
* Health insurance
* Use of methadone maintenance

Reviewed other issues:

* Primary Study Outcome:
  + Biochemically confirmed prevalence abstinence rates after 6 weeks of gum use and at end of pregnancy.
* Other Major Endpoints
  + Birth weight (< 2500 g)
  + Measures of smoking reduction
* IRB and Informed Consent
* Conducted under Investigational New Drug (IND) Application by the FDA
* Independent Data and Safety Monitoring Board to review efficacy rates and adverse events

Search Strategy: based on clinical scenario and well built question

* Patient population: pregnant
* Intervention: nicotine gum
* Comparison: none or placebo
* Outcome: birth weight, safety, efficacy
* Type or question: therapy
* Type of study: RCT

Is the study valid?

1. Assignment randomized?
2. Were all subjects entered accounted for at end of trial?
3. Were patients, clinicians, and study personnel blinded to treatment allocation?
4. Were groups similar at start of trial?
   * Inclusion and Exclusion Criteria
   * Baseline characteristics (age, ethnicity, education, prior substance abuse, mental health)
5. Aside from experimental intervention were the groups treated equally?

What are the results of the study?

* Was there a difference?
* No difference in primary outcome of decreasing smoking abstinence, though smoking amount did decrease
* Birth weights were increased
* Fewer preterm infants
* If so, how large?
* Was it statistically significant?
* 9-fold decrease in low birth weights 3287g vs. 2950g (p<0.001)
* 2-fold decrease in preterm delivery ) (p=0.027)
* Was it clinically significant? You decide
* Relative risk (RR); RR reduction; absolute risk reduction, number needed to treat to prevent one adverse outcome.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Low Birth Weight |  |  |  |
|  | Yes | No | Risk of Outcome |
| Nicotine  (97) | 2  (a) | 95  (b) | Y=a/(a+b) =  0.02 |
| Control  (87) | 16  (c) | 71  (d) | X=c/(c+d)  = 0.18 |

Treatment effect:

* Relative Risk (RR) = Y/X = 0.11
* RR Reduction (RRR) = 1- Y/X x 100 = 89%
* Absolute Risk Reduction (ARR) = X - Y =16 %
* Number Needed to Treat (NNT) to prevent one adverse outcome

= 1/(X - Y) = 1/0.16 = 6.25 patients.

16 of each hundred patients treated will benefit. (100/16 = NNT)

Y = Risk in treated = 0.02;

X = Risk in controls = 0.18

5) the patient

- Applicability:

* Article meets criteria of validity, with caveats
  + Trial stopped early because differences in primary endpoint were not great enough to be proven with planned sample size. (Primary endpoint not met)
  + Nicotine group attended more of counseling sessions
  + Overall follow-up < 65%)
* Was population similar enough to case
* Are there Qualifiers?
  + Need to measure cotinine blood levels to avoid excessive nicotine exposure
  + Needs to be combined with counseling.
  + Was it really double blind (Nicotine withdrawal effect)
* What patient needs to know
  + Benefits
  + Risks

6) Self Evaluation

* Did the process tell me what I needed to know to help the patient?
* What might I have done differently?
* Were there other sources I should have used?
* Did I take enough of the patient’s characteristics (physical, social, psychological, financial, ethnic) into consideration?
* Did the patient feel helped by what was done?

Case example 2:

1) the patient

* 76 year old Hispanic woman whose husband recently died from stroke, having trouble controlling her type II DM
* BP 130/85, BMI = 32, Heart – Mitral regurgitation. 1+ pitting edema of ankles
* LDL Cholesterol = 110 mg/dL, Total Cholesterol 190; C-reactive protein (CRP) = 4.3 mg/L, Creatinine 2.1 mg/dL
* Prescribed NTG for presumed angina and takes on an as needed basis; also ASA-81 mg/day, but no statin
* TV has touted benefits of Crestor and she wants to know if she should start.

2) the question

* Would you prescribe a statin drug to reduce the risk of myocardial infarction in
  + a 76 year old woman with Type II DM and unstable angina who has normal blood pressure, a BMI of 32\*, “normal” LDL Cholesterol, elevated CRP.

Key Fact: ½ of all MI’s and strokes occur in apparently healthy persons with LDL cholesterol below usual recommended threshold for treatment.

\* BMI > 30 classified as obesity.

3) the resource

Search Strategy:

* Patient population: Men and Women
* Intervention: Statin drug
* Comparison: placebo
* Outcome: Decreased risk of MI
* Type or question: therapy
* Type of study: RCT

Rosuvastatin to prevent vascular events in men and women w/ elevated CRP

* 17,802 apparently health men and women with LDL cholesterol levels <130/dL and C-reactive protein > 2 mg/L randomized to rosuvastatin 20 mg daily vs placebo
* Inclusion: Men >50, Women >60, no history of CV disease, LDL < 130, CRP >2
* Exclusion: Prior or current lipid lowering Rx, hormone replacement therapy, hepatic dysfunction, renal dysfunction, diabetes, SBP >190 or DBP >100, cancer, lupus, inflammatory bowel disease, severe arthritis, immunosuppressants.

Study objectives: other issues

* Primary Study Outcome:
  + First major cardiovascular event (MI, CVA, Unstable angina, CV death)
* Other Major Endpoints
  + Arterial revascularization
  + Hospitalization for unstable angina, death from any cause, time to components of major CV events
* Data and Safety Monitoring Board
* Goal: 90% power to detect 25% reduction in rate of primary endpoint with p=0.05

4) Evaluation

As before, ask if the study is valid and what are the results of this study

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | First Major Cardiovascular Event (by 2 years) |  |  |  |
|  | Yes | No | Risk of Outcome |
| Rosuvastatin  (8901) | 142  (a) | 8759  (b) | Y=a/(a+b) =  0.016 |
| Control  (8901) | 251  (c) | 8650  (d) | X=c/(c+d)  = 0.028 |

Treatment effect:

* Relative Risk (RR) = Y/X = 0.57
* RR Reduction (RRR) = 1- Y/X x 100 = 43%
* Absolute Risk Reduction (ARR) = (X – Y) x 100 =1.2 %
* Number Needed to Treat (NNT) to prevent one adverse outcome (over median follow-up of 1.9 years)= 1/(X - Y) = 1/0.012 = 83 patients. Over 4 years = 39 patients. Over average 5-year treatment – 31 patients.

Y = Risk in treated = 0.016

X = Risk in controls = 0.028

Other outcomes:

* Death from any cause – 198 vs 247
  + Rate = 1 vs. 1.25 per 100 person years or 1% vs 1.25% chance of dying each year in population studied (Median age 66)

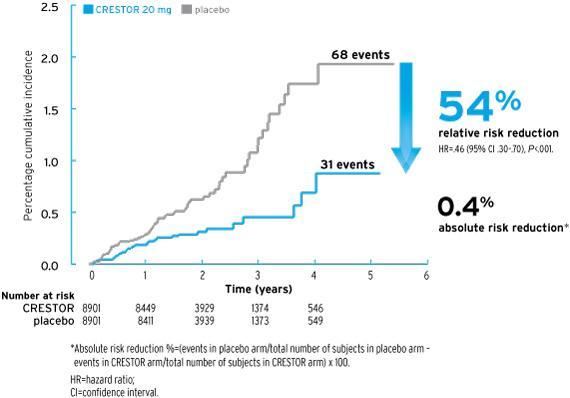
5) the patient

Applicability:

* Article meets criteria of validity?
  + Baseline characteristics balanced
  + Patients and Researchers blinded
  + 75% continued to take study pills at end of study
* Patient Hispanic
* Age 76 Type II diabetes
* History of angina,
* Creatinine 2.1,
* Unknown c-reactive protein
* Took aspirin
* ? Population similar enough to case
  + Eligibility criteria for study included
    - No history of CV disease, No diabetes, Creatinine <2
    - LDL < 130 mg/dl, CRP 2 mg/liter or more
  + Only 13% Hispanic; only 17% on aspirin
  + Only 25% over age 71

What patient needs to know:

* Benefits - ? Whether it would help to let her know the limits of your confidence that research would support her taking the drug
* Risks – No increase in myopathy, hepatic injury, cancer, disorders of hematologic, gastrointestinal, hepatic or renal systems.
* Study sponsored by Astra-Zeneca, but played no role in conduct of analyses or drafting manuscript.
* Several of authors receive payments from sponsor.



Case 3: pradaxa for A-fib

Nomar striken 82yo woman w/ permanent A-fib for 3y. 2 TIAs in that time. Her primary care physician gave her baby aspirin bc of the TIAs and warfarin after onset of A-fib to reduce risk of stroke, but her INR (international normalized ratio) has been hard to keep in therapeutic range (2-3) making weekly blood draws necessary. This is inconvenient since she does not drive bc of cataracts and nervousness. She increasing hip pain, which has resulted in unsteadiness of gait and a tendency to fall when out and about.

She has seen TV ads for Pradaxa and asks her doc to switch from warfarin to Pradaxa. Pt is overweight and doc takes CBC and other profile to be safe. Creatine clearance is 32, Hgb is 11g/dL w/ a MCV of 78.

- The study: RE-LY study in NEJM, Pradaxa vs Warfarin

* Study is valid (We will assume this)
* Results
  + In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.
  + Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

\*The Randomized Evaluation of Long-Term AnticoagulationTherapy (RE-LY)

Other issues to consider before recommendation:

* Degree of benefit in randomized trial
* Patient age
* Renal function
* Microcytic anemia (possible GI Bleeding)
* Obesity
* Hip pain and history of falls
* Lack of reversibility of direct thrombin inhibitor
* Patient convenience and cost
  + Direct drug cost and cost of testing
* How about Conflict of Interest; Marketing strategies?
  + Supported by a grant from Boehringer Ingelheim.
  + Potential Conflicts
    - Dr. Connolly reports receiving consulting fees, lecture fees, and grant support from Boehringer Ingelheim;
    - Dr. Ezekowitz, consulting fees, lecture fees, and grant support from Boehringer Ingelheim and Aryx Therapeutics, consulting fees from Sanofi-Aventis, and lecture fees and grant support from Portola Pharmaceuticals;
    - Dr. Yusuf, consulting fees, lecture fees and grant support from Boehringer Ingelheim
* Pradaxa $3000/y, warfarin is $200 for generic/y

Bleeding risk in Frail elderly

* 44 elderly patients – 2/3 over age 80 (< 1/3 in RE-LY)
* 50% weighed less than 60 kg (< 1/3 in RE-LY)
* Often with moderate to severe renal impairment (< 1/5 with CrCl < 50 mL/min in RE-LY)
* Dose not adjusted with severe renal impairment (CrCl 15-30 mL/min) (50% decrease recommended)

Big thing is that there is no reversal agent for Pradaxa; eg of old person that died after fall bc of it

Summary:

* Try to follow the 6-step process, starting with the patient oriented problem
* Be careful in formulating the question, so that your search finds relevant articles
* Read the article carefully to be assured of its its validity (closeness to the truth) and applicability (usefulness to specific patient and in more general clinical practice)
* Evaluate to see whether there might be conflict of interest on the part of the authors and whether this should affect your interpretation of results
* Return to the patient. Integrate that evidence with clinical expertise, patient preferences and apply it to practice
* Evaluate yours and the patient satisfaction with the process and plan.
* Continue to follow the scientific and lay literature for additional information that may have an impact on your ongoing decisions for this and future patients.